Increased Plasma and Platelet to Red Blood Cell Ratios Improves Outcome in 466 Massively Transfused Civilian Trauma Patients

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Objective: To determine the effect of blood component ratios in massive transfusion (MT), we hypothesized that increased use of plasma and platelet to red blood cell (RBC) ratios would result in decreased early hemorrhagic death and this benefit would be sustained over the ensuing hospitalization.

Summary Background Data: Civilian guidelines for massive transfusion (MT ≥10 units of RBC in 24 hours) have typically recommend a 1:3 ratio of plasma:RBC, whereas optimal platelet:RBC ratios are unknown. Conversely, military data shows that a plasma:RBC ratio approaching 1:1 improves long term outcomes in MT combat casualties. There is little consensus on optimal platelet transfusions in either civilian or military practice. At present, the optimal combinations of plasma, platelet, and RBCs for MT in civilian patients is unclear.

Methods: Records of 467 MT trauma patients transported from the scene to 16 level 1 trauma centers between July 2005 and June 2006 were reviewed. One patient who died within 30 minutes of admission was excluded. Based on high and low plasma and platelet to RBC ratios, 4 groups were analyzed.

Results: Among 466 MT patients, survival varied by center from 41% to 74%. Mean injury severity score varied by center from 22 to 40; the average of the center means was 33. The plasma:RBC ratio ranged from 0 to 2.89 (mean ± SD: 0.56 ± 0.35) and the platelets: RBC ratio ranged from 0 to 2.5 (0.55 ± 0.50). Plasma and platelet to RBC ratios and injury severity score were predictors of death at 6 hours, 24 hours, and 30 days in multivariate logistic models. Thirty-day survival was increased in patients with high plasma:RBC ratio (≥1:2) relative to those with low plasma:RBC ratio (<1:2) (low: 40.4% vs. high: 59.6%, $P < 0.01$). Similarly, 30-day survival was increased in patients with high platelet:RBC ratio (≥1:2) relative to those with low platelet:RBC ratio (<1:2) (low: 40.1% vs. high: 59.9%, $P < 0.01$). The combination of high plasma and high platelet to RBC ratios were associated with decreased truncal hemorrhage, increased 6-hour, 24-hour, and 30-day survival, and increased intensive care unit, ventilator, and hospital-free days ($P < 0.05$), with no change in multiple organ failure deaths. Statistical modeling indicated that a clinical guideline with mean plasma:RBC ratio equal to 1:1 would encompass 98% of patients within the optimal 1:2 ratio.

Conclusions: Current transfusion practices and survival rates of MT patients vary widely among trauma centers. Conventional MT guidelines may underestimate the optimal plasma and platelet to RBC ratios. Survival in civilian MT patients is associated with increased plasma and platelet ratios. Massive transfusion practice guidelines should aim for a 1:1:1 ratio of plasma:platelets:RBCs.

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Uncontrolled hemorrhage after both civilian and combat traumatic injury is the most common cause of potentially preventable death.[1–5] As opposed to the other major causes of traumatic death, [head injury and multiple organ failure (MOF)], hemorrhagic deaths occur quickly, usually within 2 to 6 hours of injury and often require massive transfusion (MT) (≥10 units of RBCs in 24 hours).[6–9] Therefore, any effective resuscitation strategy designed to complement rapid surgical or angiographic hemostasis must occur early.[10–14] Current resuscitation algorithms that support the sequential use of crystalloids, followed by red blood cells (RBCs) and then plasma and platelet transfusions have been in widespread use since the 1980s and are codified in the Advanced Trauma Life Support manual.[15] Recently, the damage control resuscitation strategy, equally focused on halting and/or preventing the lethal triad of coagulopathy, acidosis, and hypothermia, has challenged traditional thinking on early resuscitation strategies.[16–18] Damage control resuscitation advocates

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transfusing earlier and increased amounts of plasma and platelets along with the first units of RBCs while simultaneously minimizing crystalloid use in patients who are predicted to require a MT.[16–18]

Because coagulopathy was believed to develop from dilution and hypothermia over the course of several hours, standard resuscitation approaches emphasize the use of crystalloids and RBCs to improve cardiac output and oxygen delivery.[19,20] The use of plasma and platelets is reserved for patients with persistent hypotension unresponsive to crystalloid infusion, transfusion >6 units of RBCs, documented abnormal coagulation laboratory parameters, or obvious microvascular bleeding.[20] In 2003, Brohi et al and MacCloud et al separately described the early coagulopathy of trauma that is present on admission to the emergency department (ED) in 25% of patients and associated with increased mortality.[21,22] With this new information in mind, clinicians treating combat injuries in Iraq and Afghanistan documented improved outcomes after MT, using nontraditional resuscitation strategies.[23] This military experience suggested that an increased plasma:RBC ratio would both decrease early hemorrhagic death and improve long term survival. The lack of large controlled studies or even retrospective studies with comparison groups has perpetuated a wide variability among centers in massive transfusion protocols. Classic resuscitation strategies have been called into question by 5 recent findings: (1) recent data documenting the adverse effects of excessive crystalloid use,[24–29] (2) patients in shock are coagulopathic upon admission to the emergency department and have increased mortality,[21,22] (3) MT patients represent a small percentage of admissions (3%), yet have a 30% to 60% mortality,[30,31] (4) truncal hemorrhage represents a major cause of potentially preventable death,[1–5] and (5) severely injured trauma patients are persistently coagulopathic upon arrival to the intensive care units (ICUs).[32] Although these findings have been explored in several recent studies, there is still no broad consensus on optimal plasma and platelet ratios for civilian trauma patients.[33–39] For those patients who present in shock and are predicted to require MT, a change from the classic resuscitation approach is in order.

For massively transfused combat trauma patients, increased plasma:RBC ratios of >1:2 have been associated with improved long term outcomes.[23] However, an optimal plasma and platelet to RBC ratio has not been defined for civilian trauma patients. Our objective was to describe the present MT practices at level 1 trauma centers and to identify the optimal combination of plasma, platelets, and RBCs after civilian trauma. We hypothesized that increased plasma and platelet to RBC ratios would result in decreased early hemorrhagic death and that this benefit would be sustained over the ensuing hospitalization.

METHODS

Data for this study came from a retrospective multicenter Institutional Review Board approved trial of transfused trauma patients admitted to 16 level 1 trauma centers between July 2005 and June 2006. Included in the study were adult trauma patients who arrived from the scene and received at least 1 unit of RBC in the ED, irrespective of mechanism of injury. Of the 1574 patients in the study, 467 received a massive transfusion (MT, ≥10 units of RBCs in 24 hours). To remove the bias that may have been introduced by plasma or platelet unavailability, all patients who died within 30 minutes of arrival to the ED were excluded (n = 1). Demographic, transfusion, laboratory, time-to-death after ED admission, and outcome data were collected from each site in a uniform format and entered into a database at the Department of Epidemiology and Biostatistics, University of Texas Health Science Center, San Antonio, TX. All time-to-death data were calculated based on the time of admission to the ED. Units of RBCs, platelets, and plasma were adjusted to standard units and totaled at 6 and 24 hours after admission. Crystalloid and colloid amounts were similarly recorded. Ventilator, ICU, and hospital-free days were calculated based on a stay of 30 days. Cause of death was categorized as multiple organ failure, truncal hemorrhage, head injury, airway problems, or others, and validated by the senior investigator at each site. The initial plasma:RBC ratios and platelets:RBC ratios were determined based on the data from previous publications.[19,23,40] Data integrity was personally verified by one of the authors (KW).

The mean ± SD of continuously distributed outcomes and the number and percent, n (%), by level of binary outcomes were tabulated by category of plasma:RBC ratio (low: <1:2, high: ≥1:2) and platelet:RBC ratio (low: <1:2, high: ≥1:2). The study cohort was partitioned into 4 groups based on plasma:RBC and platelet:RBC category (1: high-high, 2: high-low, 3: low-high, 4: low-low). The significance of the relationship between mortality status (survived, died) and category of plasma and platelet to RBC ratio was assessed with logistic regression models in terms of plasma:RBC ratio category, platelet:RBC category, the interaction of the plasma:RBC ratio category, and platelet:RBC ratio category (data not shown). These independent main effects and interaction models motivated the data summaries shown. The relationship between survival time and plasma and platelet RBC ratio (group) was assessed with Kaplan-Meier plots and log-rank testing. To address the need for recommended plasma:RBC ratios in future applications of these results, we empirically estimated a target mean plasma:RBC ratio so that 98% of the values would exceed 1:2 by modeling the distribution of the ratio as $\gamma[r]$ and setting the 0.02 quantile equal to 0.5 (or, equivalently, plasma:RBC = 1:2). With this approach we assumed that subsequent to new clinical guidelines, the ratio distribution would shift to the right by an amount (Δ). The mean of the new distribution (the target mean) would then be the mean before the guidance (μ) plus the shift, giving a target mean of $\mu + \Delta$. The shift parameter, Δ, was chosen so that the lower 0.02 quantile of the modeled distribution would be approximately 0.5. We investigated heterogeneity in relation between survival to 30 days and ratios (plasma:RBC or platelet:RBC) with center using the following: (a) least squares regression of the proportion surviving 30 days within center in terms of the mean ratios within center and (b) an accelerated failure time model of time-to-death in terms of center, the ratios, covariates, and first-order interactions. All statistical testing was 2-sided with a significance level of 5%, and SAS version 9.1.3 for Windows (SAS Institute, Cary, NC, 2004) was used through-

out. All graphical presentations were created using R version 2.6.1.

RESULTS

Of the 1574 patients who received at least 1 unit of blood, 467 were massively transfused. After excluding 1 patient who died within 30 minutes of admission, the study population was 466 patients (Table 1). The mean injury severity score (ISS) varied by center from 22 to 40; the average of the center means was 33. Survival varied by center from 41% to 74%. Using least squares regression the proportion surviving 30 days varied significantly with the mean plasma:RBC ratio ($P = 0.05$, Fig. 1). After adjustment for plasma:RBC (continuously distributed), ISS, and platelets, significant variation in the time-to-death with center was found ($P = 0.02$, $df = 15$, data not shown), documenting a significant center effect (Fig. 1). No significant correlation between survival and platelet:RBC ratio with center was found.

TABLE 1. Demographic Characteristics for MT Patients

Characteristic	Total
N	466
Overall survival	59%
Age (yr)	39 ± 18
Men (%)	76
Blunt injury, (%)	65
Admission SBP (mm Hg)	107 ± 33
Heart rate (bpm)	114 ± 28
Admission base deficit	−11.7 ± 7.7
pH	7.2 ± 0.2
INR	1.6 ± 0.9
Admission temperature (°C)	36 ± 1.3
Admission GCS	9 ± 5
Injury severity score	32 ± 16

SBP indicates systolic blood pressure; INR, international normalized ratio; GCS, glasgow coma score.

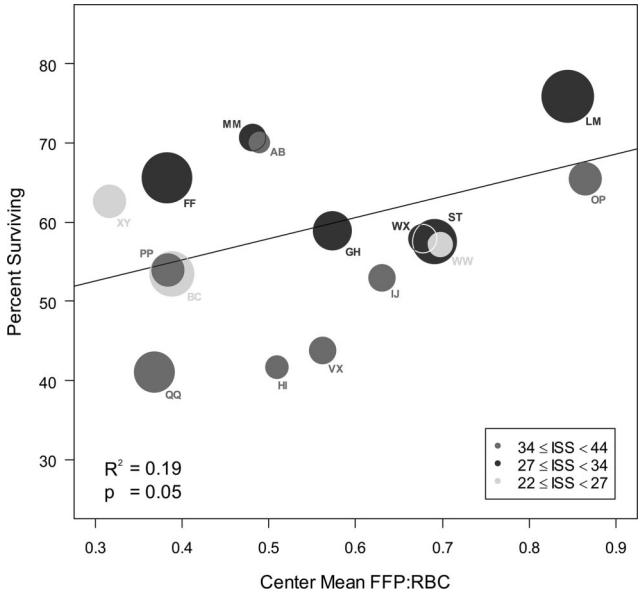

FIGURE 1. Bubble plot of the relationship of mean center plasma to RBC ratio to survival. Size of circles represents the percentage of MT patients contributed by each center. Colors indicate 3 levels of injury severity scores.

The patient plasma:RBC ratio ranged from 0 to 2.89 (mean ± SD: 0.56 ± 0.35), and the platelets:RBC ratio ranged from 0 to 2.5 (0.55 ± 0.50). A plasma:RBC ratio of ≥1:2 was associated with improved 30-day survival (40.4% vs. 59.6%, $P < 0.01$). Similarly, a platelet:RBC ratio of ≥1:2 was associated with improved 30-day survival (40.1% vs. 59.9%, $P < 0.01$). Plasma and platelet to RBC ratios ≥1:2 were found to be optimal. Plasma and platelet to RBC ratios were independent predictors of death at 6 and 24 hours and 30 days. These 2 treatment groups were then expanded into 4 in a 2-by-2 factorial layout (Table 2). Group 1 was the patients receiving the following: (1) high plasma and platelet ratio (n= 151); (2) high plasma and low platelet (n = 101); (3) low plasma and high platelet (n = 83); and (4) low plasma and low platelet ratio (n = 131). The 30-day survival was 59%, and within group survival was: group 1 = 73%; group 2 = 54%; group 3 = 67%; and group 4 = 43%, ($P < 0.001$). Kaplan-Meier analysis showed that a significant separation of groups occurred within 6 and 24 hours ($P < 0.001$) and that group 1 had increased survival compared with the others at 6 and 24 hours ($P < 0.001$, Fig. 2). The overall 24-hour difference was sustained through 30 days ($P < 0.001$, Fig. 3); however, at 30 days there was no difference between groups 1 and 3 ($P = 0.08$).

Patients were severely injured, acidotic, and coagulopathic on admission (Table 1). Although several demographic variables were different between groups, these differences were scattered between the groups and were not considered clinically significant (Table 2). By study design, differences were seen in administration of components between groups, although there were no differences in transfused RBCs (Table 3). The 2 groups that received high platelets demonstrated increased ventilator, ICU, and hospital-free days ($P < 0.01$, Table 4).

ISS and maximal regional abbreviated injury scores were not different between groups (Table 2). Specifically, the maximal abbreviated injury scores in the chest and abdomen were not different between groups ($P = 0.26$ and $P = 0.58$, respectively). The mortality benefit seen in group 1 was attributed to a reduction in truncal hemorrhage deaths to 10% compared with 25%, 22%, and 44% for the other groups, respectively ($P < 0.001$, Table 4). There were no significant differences in deaths because of MOF, head injury, airway problems, or other causes between groups (Table 4). Of those who died, median time-to-death (hours) between groups was different: group 1 = 35 hours; group 2 = 18 hours; group 3 = 6 hours; and group 4 = 4 hours ($P < 001$, Table 4).

In anticipation of optimal design of clinical practice guidelines for MT or even future prospective trials, a statistical model was constructed. To achieve an optimal plasma:RBC ratio (≥1:2) in 98% of massively transfused patients, a γ model and a location shift was assumed. The distribution of the plasma:RBC ratio was modeled as γ with scale and shape parameters of 0.268 and 2.09, respectively, and mean 0.56. A location shift of

TABLE 2. Demographic Characteristics by Plasma and Platelet Ratios

	High Plasma		Low Plasma		
	High Platelets (N = 151)	Low Platelets (n = 101)	High Platelets (n = 83)	Low Platelets (n = 131)	*P*
Age (yr)	36 ± 18	41 ± 18	42 ± 16	40 ± 19	0.003
Men (%)	83	76	68	74	0.06
Blunt injury (%)	60	68	71	64	0.35
Admission SBP (mm Hg)	110 ± 34	114 ± 35	101 ± 30	100 ± 31	0.005
Heart rate (bpm)	118 ± 29	114 ± 27	113 ± 26	110 ± 27	0.2
Admission base deficit (meq/L)	−12 ± 9	−10 ± 6	−11 ± 6	−13 ± 7	0.01
pH	7.2 ± 0.2	7.2 ± 0.2	7.2 ± 0.2	7.1 ± 0.2	0.35
INR	1.6 ± 0.7	1.7 ± 1	1.5 ± 1.5	1.5 ± 0.6	0.004
Admission temperature (°C)	36 ± 1	36 ± 2	36 ± 1	36 ± 2	0.09
Admission platelet count	197	208	217	211	0.46
Admission GCS	9 ± 5	8 ± 6	10 ± 6	9 ± 6	0.02
Injury severity score	30 ± 14	35 ± 18	32 ± 17	32 ± 17	0.06
Maximum head AIS	2 ± 2	2 ± 2	2 ± 2	1 ± 2	0.22
Maximum chest AIS	2 ± 2	2 ± 2	2 ± 2	2 ± 2	0.26

High plasma or platelet to RBC ratio ≥1:2. Low plasma or platelet to RBC ratio <1:2.
AIS indicates Abbreviated Injury Score.

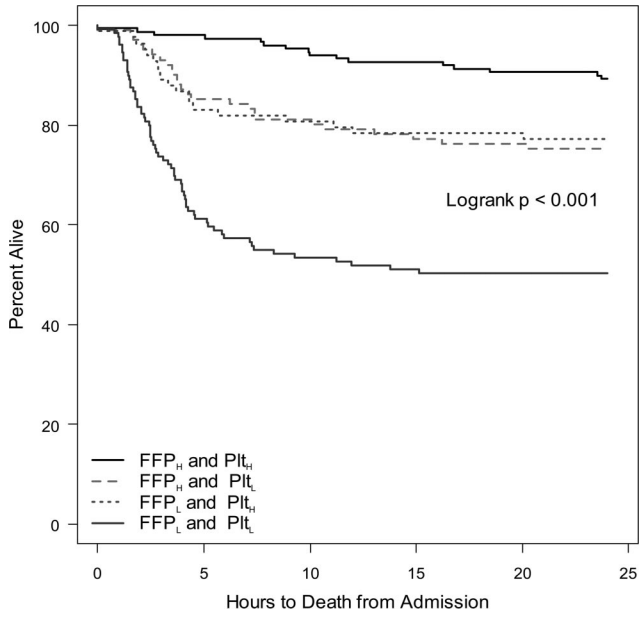

FIGURE 2. Kaplan-Meier survival plot for the first 24 hours after admission for the 4 groups (high plasma (FFP_H) or platelet (Plt_H) to RBC ratio ≥1:2, low plasma (FFP_L) or platelet (Plt_L) to RBC ratio <1:2).

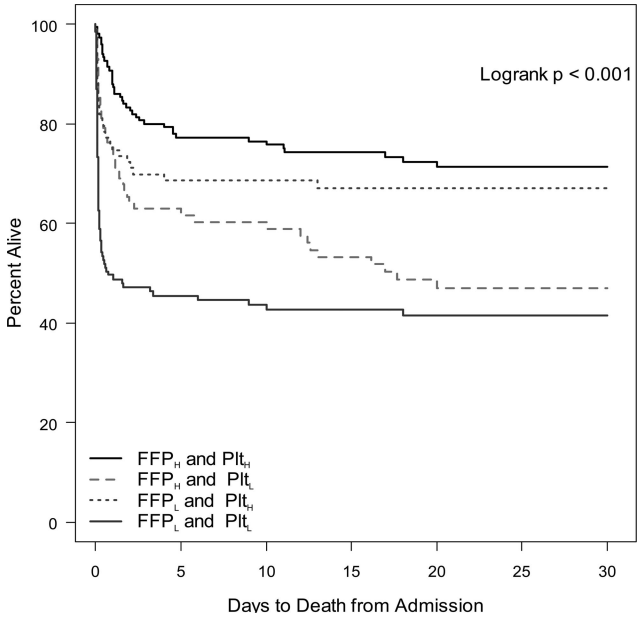

FIGURE 3. Kaplan-Meier survival plot for the first 30 days after admission for the 4 groups (high plasma (FFP_H) or platelet (Plt_H) to RBC ratio ≥1:2, low plasma (FFP_L) or platelet (Plt_L) to RBC ratio <1:2).

0.512 produced a new γ distribution with scale and shape parameters of 0.104 and 10.23, 0.02 quantile = 0.5, and mean = 1.07; for simplicity, we rounded the postshift mean to 1.0. This model suggests that if, in the future, the mean plasma:RBC ratio goal is 1:1, then approximately 98% of patients will receive a plasma:RBC ratio of at least 1:2. Thus a target mean plasma:RBC ratio of 1:1 is suggested. A corresponding target mean of 1:1 for the platelet:RBC ratio is also suggested, (data not shown).

DISCUSSION

In this multicenter MT study, the largest from level 1 trauma centers, the overall survival was 59% (range by center, 41%-74%). Overall survival within the 4 ratio groups was improved from 41% to 71% by transfusing increased amounts of plasma and platelets. These results are similar to the data from combat casualties (92% penetrating injury) showing improved survival (35%-81%) associated with increased plasma ratios.[23] Survival benefit in the present study was seen predominantly in

TABLE 3. Blood Component Transfusions by Plasma and Platelet Ratios

	High Plasma		Low Plasma		
	High Platelets (n = 151)	Low Platelets (n = 101)	High Platelets (n = 83)	Low Platelets (n = 131)	*P*
FFP (units)	17 ± 12	16 ± 10	7 ± 5	6 ± 6	<0.001
Platelets (units)	20 ± 16	5 ± 6	18 ± 10	4 ± 6	<0.001
RBC (units)	22 ± 17	21 ± 12	21 ± 11	21 ± 12	0.91
Crystalloid (L)	14 ± 10	13 ± 7	17 ± 12	11 ± 10	<0.001
FFP:RBC ratio	0.8 ± 0.3	0.8 ± 0.3	0.3 ± 0.1	0.2 ± 0.1	<0.001
Platelet:RBC ratio	0.9 ± 0.4	0.2 ± 0.2	0.9 ± 0.4	0.1 ± 0.2	<0.001
Crystalloid:RBC ratio	0.8 ± 0.5	0.8 ± 0.6	0.9 ± 0.6	0.6 ± 0.5	<0.001
Received rFVIIa (%)	34 (22)	11 (11)	21 (25)	15 (12)	0.006

High plasma or platelet to RBC ratio ≥1:2. Low plasma or platelet to RBC ratio <1:2.
FFP indicates fresh frozen plasma.

TABLE 4. Survival, Cause of Death, and Clinical Outcomes by Plasma and Platelet Ratio

	High Plasma (%)		Low Plasma (%)		
	High Platelets (n = 151)	Low Platelets (n = 101)	High Platelets (n = 83)	Low Platelets (n = 83)	*P*
Survival (%)	71	52	66	41	<0.001
Survival at 6 h	98	86	83	58	<0.001
Survival at 24 h	87	75	77	50	<0.001
Survival at 30 d	73	54	68	43	<0.001
Median time-to-death, (hours)	35	18	6	4	<0.001
Cause of death					
Truncal hemorrhage (%)	10	25	22	44	<0.001
Head injury	13	15	6	14	0.3
MOF	5	7	6	3	0.45
Airway	0	1	2	2	0.24
Other	3	6	4	4	0.85
Clinical outcomes					
Hospital-free days	6 ± 8	3 ± 6	5 ± 8	3 ± 7	<0.001
ICU-free days	5 ± 7	3 ± 6	6 ± 7	4 ± 7	<0.001
Ventilator-free days	6 ± 8	2 ± 5	7 ± 8	4 ± 7	<0.001

High plasma- or platelet-to-RBC ratio ≥1:2. Low plasma- or platelet-to-RBC ratio <1:2.

patients with truncal hemorrhage, with most of the improvement seen by 6 hours.

Trauma patients largely die of truncal hemorrhage, head injury, or MOF. Overall survival rates of patients admitted to civilian trauma centers are approximately 96%. Those who do not receive a transfusion have a survival of >99%, whereas the 2% that are massively transfused have a survival of ≈60%.[30,31] Autopsy studies demonstrate that uncontrolled truncal hemorrhage is responsible for 45% to 85% of potentially preventable death.[1–5] Hemorrhagic truncal death after admission occurs very quickly and prolonged shock increases MOF and late death.[8,41] Therefore, new resuscitation paradigms must be implemented to improve outcomes from truncal hemorrhage.

After World War II it was recognized that hemorrhagic shock was optimally treated with whole blood replacement.[42] However, in 1976, Carrico et al stated that the optimal resuscitation of hemorrhagic shock patients consisted of 1–2 L of lactated ringers, accompanied by whole blood transfusion over the first 45 minutes after ED arrival.[43] By the mid 1980s plasma, platelets, and cryoprecipitate had been removed from red cells, yet resuscitation strategies for patients in hemorrhagic shock had not been changed to account for the new blood components, focusing on rapid infusion of warm crystalloid and RBCs. We continued to transfuse RBC units as if they were whole blood, and increasingly large amounts of crystalloid were used to maintain blood pressure and oxygen delivery.[44,45] Neither RBCs nor crystalloid contain procoagulant components and this practice has likely exacerbated the early coagulopathy of trauma. There were no large prospective studies of these changes in transfusion products or practices, and the retrospective studies did not construct comparison groups to examine different amounts or ratios of the various blood products.[46–48] Concomitant to the changes in component therapy and increased crystalloid use, acute respiratory distress syndrome, and abdominal and extremity compartment syndromes were reported with increas-

ing frequency, whereas damage control surgery strategies evolved to manage coagulopathic bleeding.[49–51] It is likely that some of acute respiratory distress syndrome and much of the compartment syndromes represent iatrogenic injury and can be prevented by more appropriate use of crystalloids and blood component therapy.[24,52–55]

In 2003, Brohi et al and MacCloud et al demonstrated that 25% of trauma patients arriving in the ED are coagulopathic, (defined by prolonged prothrombin time or partial thromboplastin time) and have increased mortality.[21,23] Based on mathematical modeling, recommendations were also made that increased ratios of plasma and platelets to RBCs (2:3) should be used to prevent iatrogenic hemodilution and progressive coagulopathy.[56,57] Subsequently, Gonzalez et al recommended that increased plasma be used earlier in trauma resuscitation, based on persistent coagulopathy associated with increased mortality.[32] Finally, reprising the editorial by Moore and Shires in 1967 asking for moderation in the use of crystalloid,[58] multiple authors have recently described the proinflammatory characteristics of crystalloid.[25–28] Others have described decreased abdominal compartment syndrome and death[24] or increased ventilator and ICU-free days[29] simply by limiting the amount of crystalloid infused early after admission. Interestingly, plasma has been shown to be less inflammatory than artificial colloid, albumin, or lactated ringers in a swine study of hemorrhagic shock.[28] In the current study, patients in groups 1 and 3 received more overall crystalloid, but because of their longer survival over 24 hours the rate of infusion was likely higher in groups 2 and 4. Moore et al recently summarized many of these concepts and commented on the potential changes in outcomes that could occur simply by altering the rates and amounts of resuscitation fluids.[59,60] Many authors have focused on altering rates and amounts of crystalloids.[60–64] We feel that the same successful approach should be applied to blood products.[23,65–71]

Recent reviews of massive transfusion protocols for trauma patients in the United States and Europe recommend plasma to RBCs ratios between 1:1 to 1:2.[17,18,72,73] The potential benefits of increased plasma use in the MT population likely come from several areas, including replacing coagulation proteins, which prevents or treats the coagulopathy associated with hemorrhage and shock.[74–77] Although the improved outcomes associated with decreasing crystalloid and increased plasma and platelets use in coagulopathic patients makes intuitive sense, we do not suggest that the observed improvement in mortality is simply a reversal or prevention of early coagulopathy alone. It is likely that differences in injury, endothelial structure, alterations in thrombomodulin and protein C, adhesion, systemic inflammation, consumption, hemodilution, acidosis, hypothermia, hypocalcemia, fibrinolysis, increased platelet counts and plasma proteins, genetic variation, and many other mechanisms are important.[78–80]

Each unit of plasma contains approximately 400 mg of fibrinogen, an essential protein for clot formation shown to decrease early in patients with hemorrhage.[80–83] Plasma also has the additional benefit of acting as a buffer, potentially improving the acid base status of patients who are already acidotic.[84] This is in contrast to the use of crystalloids that are acidic in nature and proinflammatory.[26,27] Lastly, plasma and RBCs are both excellent volume expanders. As the risk of blood-borne diseases becomes ever smaller, the increased use of plasma as a volume expander in the small percentage of patients requiring MT seems indicated, reserving RBCs to treat oxygen debt and crystalloid as a smaller component of the resuscitation algorithm.

Improved outcomes after earlier transfusion of increased amounts of blood products are documented in 2 retrospective studies.[23,71] Johansson et al reported that increased amounts of plasma and platelets given in the operating room in predetermined ratios for patients with ruptured aortic aneurysms improved survival (44% vs. 66%, $P < 0.05$).[71] A platelet count of $>100 \times 10^9$ upon arrival in the ICU was associated with improved survival. The survival difference appeared in the first 4 days and was sustained through 30 days, ($P < 0.02$). Borgman et al described their improved results in combat trauma patients by transfusing increased amounts of plasma.[23] They compared outcomes of similarly injured patients who received varying ratios of plasma:RBCs. In ratios approaching 1:1, long term mortality was 19%, 1:3 was 35%, and 1:8 was 60% ($P < 0.05$). Time-to-death was 2 to 4 hours and largely from truncal hemorrhage in the 2 groups receiving less plasma. Platelet transfusions were not routinely available in the combat theater during the data accrual period. Questions remained if similar results would be seen in a civilian trauma population, with different injury patterns, increased comorbidities, and without fresh whole blood transfusions. These important papers by Johansson et al[71] and Borgman et al[23] have sparked a renewed interest in the use of new combinations of existing blood components and more data are forthcoming.[33–39]

These papers have brought to the forefront the controversial issue of predetermined ratios for use in the early massive transfusion of trauma patients.[85–87] Although, ideally, every product transfused would be based on a laboratory value and real time expert consultation with transfusion specialists, this is simply not possible in the rapidly bleeding hemorrhagic shock patient. Unfortunately, without a well-defined massive transfusion protocol, inadequate amounts of plasma and platelets are frequently transfused, with the patient suffering the negative consequences.[86,87] In recognition of the many and varied human and logistical factors involved in delivering the appropriate ratio of products, many centers have developed a "push" rather than a "pull" approach.[68] Essentially, this means streamlining administrative tasks and paperwork to deliver blood products as quickly as possible. Once initiated, this approach keeps fixed ratios of plasma, platelets, and RBCs coming from the blood bank to the bedside until stopped by the clinician, ensuring that appropriate ratios and quantities are transfused. Once established, through careful discussion with all parties involved in massive transfusion, this system works well.

Dilutional thrombocytopenia (platelet counts $< 100 \times 10^9$/L) as the major cause of microvascular bleeding, has tended to develop only after MT patients received 18-20 units of stored whole blood.[88–90] In addition to thrombocytopenia, intrinsic platelet function is impaired by acidosis and hypothermia, which can develop in severely injured patients who require MT.[91–93]

The currently recommended platelet transfusion threshold is 50 to 100 $\times$ 10^9/L in actively bleeding patients.[94,95] The importance of platelets in MT was studied in a single randomized trial that noted no difference in microvascular bleeding, though the platelet group received a low platelet:RBC ratio of 0.5:1.[96] Later studies found that a 0.8:1 ratio was associated with improved survival.[19,40,56,57] In summary, the available data are sparse on when platelets should be started and the optimal ratio. However, when comparisons are made, a ratio approaching 1:1 is associated with improved survival.

Most expert recommendations are based on level IV data from elective surgery patients, and suggest guiding transfusions based on laboratory values. Unfortunately, most of these critical laboratory threshold values occur after a blood loss equaling 1.5 to 2 blood volumes.[97–100] It is interesting that many of the patients in the current study were coagulopathic upon arrival (international normalized ratio >1.5) and met the laboratory definition for requiring plasma transfusion upon arrival in the ED. Additionally, given the rate of resuscitation in MT trauma patients, laboratory parameters can rarely be used to guide blood component therapy. Rather, their need is judged clinically, highlighting the need to adhere to established MT protocols.[87]

To our knowledge these data represent the first to report outcomes of plasma and platelet transfusion together. Based on data from others describing survival benefit by transfusing more versus less plasma and platelets, high and low ratios were explored in the massive transfusion dataset. By comparing ratios starting at 1:1 and continuing through 1:8, we determined that survival was improved at 6 and 24 hours and 30 days with ratios >1:2 for both plasma and platelets. We explored the relationship of plasma and platelets to RBC ratios by creating 4 possible groups with the 2 components. Among ratio groups, overall survival ranged from 41% to 71%, with essentially all the difference occurring in the first 6 hours after admission because of a decrease in fatal truncal hemorrhage. Survival differences persisted through 30 days ($P < 0.001$). Despite the significantly increased plasma and platelet transfusion amounts, there was no difference in MOF as a cause of death between groups (5%, $P = 0.45$). These findings support the use of increased amounts of plasma and platelets early in the course of care in patients predicted to require massive transfusion.

Concern exists that transfusing increased amounts of plasma and platelets will increase the incidence of transfusion related acute lung injury (TRALI) and MOF.[100–104] These concerns are reasonable, but must be placed within the appropriate clinical context. Massive transfusion patients, although comprising only 3% of all trauma admissions, have a mortality of 30% to 60%, whereas TRALI occurs anywhere from 1 in 5 to 10,000 transfusions, is currently managed with ventilator support, usually resolves in 24 hours and is fatal in only 6% to 9% of cases.[103–105] Using the above numbers, there are ≈5000 trauma patients who could be saved at the risk of ≈10 cases of fatal TRALI per year. There is the obvious conundrum in this study of transfusing proinflammatory plasma and platelets that are associated with improved outcomes in critically injured trauma patients, without increased fatal MOF.

The present study has several limitations, principally those associated with a retrospective design. The 4 groups were not equal in a limited number of demographic parameters; however, these inequalities were distributed across the groups and considered clinically insignificant. The timing of the various components of the massive transfusion, (crystalloid, RBCs, plasma, and platelets) were unknown, so although the final ratios were similar within groups there may have been important differences in the order and time when the products were actually infused. Depending on the collection method, platelet units can contain a significant amount of plasma.[75] As a result, the amount of plasma that was transfused in the patients who received platelets was underestimated and may have contributed to the similar 30-day survival rates in groups 1 and 3. Although the primary end point was mortality after admission, and causes of death were defined before data collection, MOF was not explicitly defined. However, given the types of centers, lack of overlap in categories, and the broad agreement of definitions, we feel that the conclusions are valid. There was no data collected on nonfatal diagnoses, complications, infections, or procedures; however, ICU, ventilator, and hospital-free days were considered a surrogate and outcomes for the high platelet groups were improved compared with low platelet groups ($P < 0.05$). Finally, the effect of multiple unmeasured confounding variables must be considered as at least a partial explanation for the study results.

The current study has several important strengths. Our findings are in agreement with and extend the observations of other authors.[23,32–39] This study was unique because of the measurement of plasma and platelets reflecting actual clinical practice, and the availability of time and cause of death from admission and blood products in the first 6 and 24 hours. To our knowledge, these data represent the largest MT study and the first to study plasma and platelet transfusion data together along with high and low ratio comparison groups. The type of centers contributing data for this study lends validity to the conclusions, despite the retrospective study design and significant variability between centers. Survival was improved with the use of increased plasma and platelets in relation with RBC use. To ensure the beneficial 1:2 ratio is achieved 98% of the time (2 standard deviations), one should plan for a 1:1 goal of mean plasma:RBC ratio. Despite the significantly increased plasma and platelet transfusion amounts, there was no difference in MOF as a cause of death between the 4 groups. Though trauma centers are required to have a MT protocol,[106] data are sparse on which to base quality clinical practice guidelines. To maximize the benefits while minimizing the risks of using increased blood products earlier in the care of MT trauma patients, many centers are now developing and implementing MT prediction models, transfusing with defined blood product ratios and with decreased crystalloid rates. The data in the current study, together with the recent military experience, are compelling and have served to stimulate critical reexamination of current transfusion practice.

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Discussions

DR. ERNEST E. MOORE, JR (DENVER, COLORADO): Many thousands of critically wounded soldiers from the ongoing conflicts in the Middle East are alive today because of Colonel Holcomb's unique proclivity to bridge evolving trauma care strategies in civilian and military environments. As a military surgeon, John had the foresight to study damage control in the civilian trauma centers in Houston and successfully exported these principles to the battlefields of Iraq and Afghanistan, where he continues to extend the frontiers.

The current report, motivated by compelling military data, indicates a survival benefit of preemptive fresh frozen plasma given at a ratio of 1:1 with every transfused unit of red cells. Colonel Holcomb has built an impressive collaboration with 16 civilian level 1 trauma centers to test the hypothesis that presumptive platelets and FFP will improve survival in injured patients requiring a massive transfusion. Based on systematic analyses of their extensive database from 466 qualified patients, John and his colleagues conclude that a 1:1:1 ratio of FFP to platelets to red cells should be considered the standard for civilian practice.

These finding have profound implications as we struggle to develop safe and cost-effective transfusion policies, and are particularly timely in the wake of recent reports of influential journals incriminating overzealous FFP and platelet transfusion in the pathogenesis of acute lung injury. Similar to stored red cells, these blood products are expensive and contain quantities of legitimate inflammatory mediators such as activated complement and fibrin degradation products in FFP, soluble CD 40 ligand RANTES, and arachidonic in platelets. Furthermore, the composition of FFP and platelets varies considerably depending on retrieval method and storage duration.

With that brief background, I have several items for the authors to consider, although none of these will be new to these experts.

First, one of the perplexing issues of this study and other recent similar efforts is a lack of a documented mechanistic link. In the current scenario, preemptive FFP and platelets were administered to attenuate postinjury coagulopathy, yet evolving data suggest that the initial coagulopathy in severe trauma is independent of clotting factor insufficiency.

You have nicely illustrated that the separation in deaths occur within the first 3 hours. Thus, to pursue your hypothesis on a scientific basis, it would seem important to (a) analyze transfusion ratios within the first 1, 2, and 3 hours and (b) to assess the impact of these ratios on coagulation status during this critical period.

Is early improvement in coagulation function an independent variable for survival? More specifically, did patients die of uncontrollable torso blood loss that was fundamentally unrelated to their coagulation status? Perhaps the ability to achieve higher FFP and platelet ratios is simply a marker of a more favorable injury pattern. Did you exclude patients who were given activated factor VII? Was there a difference in blunt versus penetrating trauma? Did you examine the rate of red cell transfusion during the first hour of arrival?

I recall the insightful words of a blood banker, Dr. Ben Galloway, when as a junior attending I would request fresh whole blood for a trauma patient at Denver General in the 1970s and he would politely respond, "is the patient dying because they are bleeding or bleeding because they are dying?" Modern urban EMS can certainly deliver patients who are in the process of dying irrespective of our efforts. Alternatively, the benefits of early plasma may be because of other effects, such as colloidal properties or even binding lipid mediators.

This stimulating study prompts many interesting questions, but I will conclude with a focus on the future. I would respectfully review this meticulous investigation as tantamount to a well-done meta-analysis, which we have learned does not provide a definitive answer to a complex question, but rather the genesis of a hypothesis to be tested in a rigorous controlled trial.

In that light, how would you propose such a trial to determine if 1:1:1 is optimal? Will you attempt to study FFP and platelets concurrently? How do you imagine activated factor VII, because this will likely become integral in massive transfusion protocols. Will point-of-care testing of coagula-

tion status such as thromboelastography play an important role in this pivotal study?

Dr. Donald D. Trunkey (Portland, Oregon): In doing these massive transfusion protocols, there is another issue, and that is the age of the packed red blood cells. Did you look at this in this multi-institutional study? Furthermore, if you get down to common horse sense, a 1:1:1 ratio is called whole blood. Why, then, do we not give whole blood?

Dr. Howard R. Champion (Bethesda, Maryland): Colonel Holcomb's data are somewhat disturbing but are certainly supported by my own observations as chair of a Data Safety Board for an international resuscitation research initiative. The variation in clinical practice from one center to another is of great concern, as is the problem regarding control for case mix differences and confounding variables. Together these issues raise the question as to whether one can draw viable scientific conclusions from data from acute resuscitation research.

It seems we need not only to get some agreement on resuscitation protocols but also on the actual process within a trauma center by which we get timely and appropriate delivery of coagulation factors to the patient. Thus, we need to control for the therapeutics and for the complexities of injury in these patients if we are to study them successfully.

Dr. Anthony A. Meyer (Chapel Hill, North Carolina): Obviously in this, timing is everything. When you look at the data, do you have an idea about the timeliness of the fresh frozen plasma and platelets as related to the red cells? I have had personal experience with a ratio that was close to that but it was so weighted toward the end that you wind up with a patient that is profoundly coagulopathic, and by the time you pump in all the fresh frozen plasma and platelets, it is probably too late. Do you have an idea about the relative timing of the components?

Dr. John B.Holcomb (Fort Sam Houston, Texas): There is no data driven mechanism from this retrospective clinical study. We do suggest some possibilities in the paper and I think it is simplistic to assume simple replacement of coagulation factors accounts for the improvement in survival. Unfortunately, most of the animal models that we have used are fairly artificial, using lactated ringers, heparin, coumadin, or hypothermia to generate a coagulopathic state. There is no trauma and coagulopathy preclinical animal model I am aware of where shock induces the coagulopathic sate, which is what we are trying to treat.

To answer several of your questions, we have no data on the rate of infusion of any products or changes in laboratory values over the first 6 hours. This is one of the problems with performing a retrospective study. We just do not know what happened during the first 3 critical hours. We have always said that all bleeding stops one way or the other, and now we know that that time frame is 3 hours. Unfortunately, our first time point was 6 hours, so we do not know what happened in the mixture of those ratios in the first several hours. However, very few studies have even looked at the first 6 hours after admission, and based on these data we hope to accomplish a closer inspection of the first 1 to 3 hours in a prospective observation transfusion trial that should start within the next year.

There were no obvious differences between blunt versus penetrating patients, although this will be the focus of a future investigation. Recombinant factor VII-A was given in about 17% of these massive transfusions and there was no difference associated with survival.

Several of your questions and comments are thought provoking, but as you know cannot be answered based on these data. They will be important questions to address in any prospective trial, which we must do. Amazingly, there are no prospective randomized data in massively transfused patients. These retrospective data will hopefully provide the information within which to intelligently design prospective trials in the massively transfused population. We must do this study as these patients are the ones most likely to benefit, and I think that we need to understand how best to use and not use blood products.

I think the point-of-care testing in the ED is an extremely important and largely overlooked issue. The current coagulation tests we use are relatively insensitive, and others, such as the TEG will allow earlier appreciation of more subtle coagulation abnormalities. With modern machines you can obtain coagulation results in the ED in 2 minutes, and a preliminary TEG in 10. They give you much more information about what is happening in terms of coagulopathy in your patient. We now know that a quarter of the patients arrive coagulopathic within 30 minutes of injury in the emergency department and we need to focus on that issue just as we have done with hypothermia and coagulopathy. There is absolutely no reason not to know the coagulation status of your patient within minutes of their arrival.

Dr. Trunkey asked about 1:1:1 being reconstituted whole blood. It is actually worse than that. When you take whole blood and separate it into components, put it through the machines, then put it back together, a 1:1:1 ratio is actually an anemic, thrombocytopenic, and coagulopathic fluid. It does not function and whole blood when you take it out of the body, although that is the best you can do. If you add any crystalloid or colloid to the 1:1:1 solution you further dilute the blood products and exacerbate the coagulopathy in trauma. Although 1:1:1 is good, I actually think whole blood is better. Although we are aware of the issue, based on the labor required we did not calculate the age of blood in this study.

In response to Dr. Champion, the significant variation in survival (41%-71%) between centers was enlightening to me and many of my collaborators. I was assured that with sophisticated statistics the significant center effects can be accounted for, but I am not sure I am convinced. I do think these data can be used to facilitate the discussions on the need

for data driven clinical practice guidelines, especially concerning use of blood products. Rapid delivery of these blood products can be achieved. About half of the participating centers put thawed plasma in their ED so that plasma is available within minutes of the patient's arrival. The thawed plasma is being used as the primary resuscitation fluid in the small group of patients that present as acidotic and coagulopathic. This practice requires a lot of coordination between the emergency department, blood bank, surgery, anesthesia, and nurses, but it can be done.

Dr. Meyer, your question about the actual timing of infusions is very good and I think I answered it. With the current data we just do not know. Dr. Gonzalez and his group in Houston did address this in their recent Western Trauma presentation. Their final 24-hour ratios were always 1:1; however, their 6-hour ratios were closer to 1:2. Two years ago they started resuscitating their patients with 1:1 with the first unit of RBCs and improved their 6-hour ratio from 1:2 to 1:1, with an improvement in survival from 30%-15%.